PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	11-05-2005
Applicant's or agent's file reference	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FI 2005/000011	11.01.2005	28.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07K 1/00, B01D 9/02

Applicant
Macrocrystal Oy et al

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further opinions, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language, _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-11	YES
	Claims		NO
Inventive step (IS)	Claims	1-11	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-11	YES
	Claims		NO

2. Citations and explanations:

The present application relates to a method for crystallisation of proteins and peptides, characterised in that two solutions are mixed together, one of which is an aqueous solution of proteins or peptides and the other is an aqueous polymer solution, wherein the polymer is alginate, dextrin, chitosan or pectin or a hydrolysate or a mixture of any of the said polymers. Upon mixing the two solutions the protein or peptide crystallises permanently. The aim is to produce crystallised proteins which float freely in the polymer solution or continuous uniform gel, which have improved stability and which may be used in medical formulations.

Reference will be made to the following documents cited in the International Search Report:
D1) WO 9955310
D2) EP 0263490
D3) US 20020001619
D4) Pharmaceutical Research, vol 18(11): 1483-1488 (2001), Jen A & Merkle H P.

D1 relates to a process for crystallisation of proteins and stabilised protein crystal formulations. It has been found that proteins may be successfully stored in dry form for long periods of time at ambient or elevated temperatures in crystalline form. Formulations comprising the protein crystals are prepared either by (1) adding ingredients or excipients where necessary to stabilize dried crystals or (2) encapsulating the protein crystals or crystal formulations within a polymeric carrier to produce a composition that contains each crystal and subsequently allows the release of active protein molecules.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

According to D1, protein crystals may be stored either in the form of suspensions by replacing the mother liquor with a nonaqueous solvent, or in dried solid form. Non-aqueous slurries of crystalline therapeutic proteins are especially useful for subcutaneous delivery. In order to enhance the stability of the crystals, excipients such as hydroxypropyl-p-cyclodextrin may be added to the already crystallised protein in mother liquor. See page 35, line 31 - page 37, line 6; page 88, line 15 - page 89, line 14; page 94, line 1 - page 96, line 28; claims 1, 16, 50, 110 and 116.

D2 describes a sustained-release particulate preparation which comprises a polymeric compound which is capable of being degraded in the body, a pharmacologically active agent (e.g. a protein or a peptide), and a natural high-molecular weight compound of sugar origin (e.g. chitosan, pectin or dextrin). The preparation is prepared by dissolving the polymeric compound, and mixing it with the pharmacologically active agent and an aqueous solution of the compound of sugar origin, followed by stirring in order to obtain a preparation which has fine and uniform particle size. There is no indication in D2 of crystallisation of the pharmacologically active agent (see the claims).

D3 relates to sustained-release compositions comprising a hydrophilic polymer, a biologically active agent, e.g. a protein, and a precipitating agent, wherein the composition is characterised in that the biologically active agent is co-precipitated with the polymer. The polymer is for example alginate (see claims 1-10).

D4 reviews methods of crystallising proteins for use in pharmaceutical formulations.

The cited documents D1-D4 represent the general state of the art. The invention defined in claims 1-11 is not disclosed by any of these documents. The cited prior art does not give any indication that would lead a person skilled in the art to the claimed method of crystallisation of proteins. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1-11 is novel and is considered to involve an inventive step. The invention is industrially applicable.